A B C D

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Boehringer Ingelheim Pharmaceuticals, Inc.

April 29, 2009

DRUG INFORMATION

Dear Mr. Citron:

Thank you for discussing SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) with your Boehringer Ingelheim Pharmaceuticals, Regional Manager, State Government Affairs, Joe Riedl. You requested American Academy of Managed Care Pharmacy (AMCP) Dossier for review during the upcoming Pharmacy and Therapeutics Committee meeting at your institution as well as an electronic version the recent publication by Tashkin and collegues.

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SPIRIVA HandiHaler is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Any other use not included in the package insert(s) is an investigational use and cannot be recommended by Boehringer Ingelheim Pharmaceuticals, Inc.

Please find the enclosed AMCP Dossier (Clinical and HE data) and SPIRIVA bibliography. Also, attached below for your reference is additional information on the following topics:

- Use in COPD Patients with Asthma
- Cardiovascular Side Effects
- Combined with Inhaled Corticosteroids
- Formoterol Versus and in Combination with SPIRIVA
- INSPIRE Trial
- Salmeterol Plus Fluticasone Combined with SPIRIVA
- Salmeterol Plus Fluticasone Versus SPIRIVA
- UPLIFT Trial Results
- Use in Patients with Mild-to-Moderate COPD

Regrettably, an electronic version of the UPLIFT publication is not available; however the complete citation is as follows: Tashkin DP, Celli B, Senn S, Burkhart D, et al. A 4-year trial of tiotropium in Chronic Obstructive Pulmonary Disease. N Engl J Med 2008;359(15):1543-1554. The publication can be accessed at http://content.nejm.org/cgi/reprint/359/15/1543.pdf.

If you did not request this information, please contact our Drug Information Unit Call Center at 1-800-542-6257 (option #4).

Thank you for your interest in SPIRIVA HandiHaler. If you should have any further questions, please do not hesitate to contact the Drug Information Unit.

Sincerely,

The Drug Information Unit Healthcare Professional Staff

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AMACHATE/2009-012005

AMCP Dossier (Clinical and HE data)

The AMCP dossier is intended to provide clinical and outcome data that are useful for formulary review. The Drug Information Unit is available to answer questions regarding the content of this material. Please contact your Boehringer Ingelheim Pharmaceuticals, Regional Manager, State Government Affairs, Joe Riedl for the scheduling of consultations.

Bibliography

For your information, full prescribing information and a comprehensive bibliography regarding tiotropium has been enclosed.

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Tiotropium Use in COPD Patients with Asthma

Mangussen et al. performed a 12-week randomized, double-blind, placebo-controlled, parallel group trial with tiotropium 18 mcg daily. The primary objective of the trial was to demonstrate the superiority of tiotropium 18 mcg once daily administered via the HandiHaler compared to placebo in the treatment of patients with COPD and a concomitant diagnosis of asthma. The primary efficacy endpoint was the change in FEV_1 $AUC_{0\text{-}6h}$ after 12 weeks of treatment. Patients were allowed to continue usual respiratory medications except for inhaled anticholinergics. Participation was contingent upon the following inclusion criteria: diagnosis of both COPD and asthma, age $\geq$40 years, smoking history >10 pack years, post-bronchodilator FEV_1<80% predicted, FEV_1/FVC<70%, $\geq$12% and $\geq$200 ml increase in FEV_1 following inhaled bronchodilator at the screening visit or documented within the last 5 years in patient's records, and received inhaled steroids $\geq$1 year prior to study entry. At baseline and 4 and 12 weeks following randomization, spirometry was measured 30 and 10 minutes before the study drug administration and serially for 6 hrs post-dosing. Four hundred seventy two patients were randomized to tiotropium 18 mcg (228 patients) or matching placebo (244 patients). The mean age of the patient population was 59.6 years, 61.4% men, and the mean FEV_1 was 1.55 L (53.0% predicted). The mean duration of COPD and asthma was 9.2 and 43.2 years, respectively. Baseline characteristics of the two treatment groups were balanced. At 12 weeks, improvements were noted in the primary endpoint (FEV_1 $AUC_{0\text{-}6h}$ difference 186±24 ml, p<0.001) and for morning pre-dose FEV_1 (difference 98±23 ml, p<0.001). Further, significant differences in favor of tiotropium were observed for pre-dose FVC (difference 128±34 ml, p<0.001) and FVC $AUC_{0\text{-}6h}$ (difference 232±35 ml, p<0.001). Compared to baseline, the mean weekly number of daily puffs of rescue salbutamol was significantly decreased in the tiotropium arm (difference between placebo and tiotropium groups of 0.45±0.17 puffs, p<0.05). Of 472 randomized patients, 176 (37.3%) reported adverse events during the treatment period with similar frequency in the active and placebo arms. The most frequent adverse events were lower respiratory system disorders (placebo: 20.1%; tiotropium 12.7% with exacerbations being the most commonly reported), upper respiratory system disorders (placebo: 5.7%; tiotropium: 13.2%), and gastrointestinal system disorders (placebo 5.7%; tiotropium 9.6%, with dry moth being reported most commonly). The frequency of COPD exacerbations was lower in the tiotropium arm (5.7% versus 10.7% in the placebo arm) and the frequency of asthma was similar in the groups (placebo: 3.3%; tiotropium 2.6%). The investigators concluded that tiotropium is safe and effective in patients with COPD and concomitant asthma (observed spirometric improvements along with symptomatic benefit as evidenced by decreased use of rescue salbutamol). However, whether tiotropium was only treating the COPD component or had some effect on the concurrent asthma could not be discerned.

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Mangussen H et al., Improvements with tiotropium in COPD patients with asthma. *Respiratory Medicine*. 2008;102:50-56.

Cardiovascular Side Effects

During four one-year (two one-year placebo-controlled and two one-year ipratropium-controlled trials) and two six-month placebo and salmeterol-controlled pivotal clinical trials with SPIRIVA HandiHaler, the incidence of cardiac events in the system organ class (SOC) of "General Cardiovascular Disorders" (includes preferred terms such as cardiac failure, cardiomegaly, and cor pulmonale) and "Myo-, Endo-, Pericardial and Valve Disorders" (includes preferred terms such as angina, coronary artery disorder, myocardial ischemia, and myocardial infarction) was generally low and balanced between the tiotropium groups and the control groups with the exception of cardiac failure, which in the six-month trials appeared less frequently in those receiving tiotropium (no patients) compared to six patients in the salmeterol groups (1.5%) and three patients in the placebo groups (0.8%).[1,2]

In the one-year placebo-controlled trials adverse events classified as "Heart Rate and Rhythm Disorders" (include preferred terms such as arrhythmia, bradycardia, cardiac arrest, atrial fibrillation, palpitation, tachycardia and supraventricular tachycardia) occurred in 4.4% (24 patients) of the tiotropium 18 mcg group and 2.2% (8 patients) of the placebo group while in the one-year ipratropium-controlled trials the proportions were 3.9% (14 patients) in the tiotropium group and 5.0% (9 patients) in the ipratropium group. During the six-month trials, events classified as "Heart Rate and Rhythm Disorders" occurred in 2.5% (10) of patients in the tiotropium and salmeterol groups as well as 2.3% (9) patients randomized to receive placebo.

Cardiac events were responsible for a total of ten deaths in the one-year clinical trials and three deaths in the six-month trials. The incidence of select cardiac adverse events related to "General Cardiovascular Disorders", to "Heart Rate and Rhythm Disorders", as well as "Myo-, Endo-, Pericardial, and Valve Disorders" that occurred during the one-year and the six-month trials is summarized in Tables 1 through 4.

Table 1. Incidence of selected cardiac adverse events form phase III one-year trials.[1]

Cardiovascular Event	**Placebo-controlled**		**Active-controlled**	
	Tiotropium N=550	**Placebo** N=371	**Tiotropium** N=356	**Ipratropium** N=179
	%	**%**	**%**	**%**
Arrhythmia	0.7	0.3	0	0.6
Angina pectoris	0.7	0.5	1.7	2.2
Angina pectoris, aggravated	0.4	0	0.3	0.6
Atrial fibrillation	0.9	0.8	1.4	2.2
Cardiac arrest	0.2	0	0	0
Cardiac failure	0.9	1.1	0.3	0.6
Cardiac failure, right	0	0	0.6	0
Coronary artery disorder	0.7	1.1	0	0
Myocardial infarction	0.5	0.5	0.8	0.6
Tachycardia	0.7	0.3	1.1	0
Supraventricular tachycardia	0.4	0.3	0	0

Table 2. Incidence of selected cardiac adverse events form phase III six-month trials.[2]

Cardiovascular Event	**Tiotropium** N=402	**Salmeterol** N=405	**Placebo** N=400
	%	**%**	**%**
Angina pectoris	1.2	0	0.3
Angina pectoris, aggravated	0	0.5	0
Atrial fibrillation	0.5	0.7	0
Cardiac arrest	0	0	0.5
Cardiac failure	0	1.5	0.8
Cardiac failure, left	0	0.2	0
Coronary artery disorder	0	0.2	0
Myocardial infarction	0.5	1.0	0.8
Myocardial ischemia	0.2	0	0
Tachycardia	1.0	0	0.3
Supraventricular tachycardia	0.2	0.2	0
Ventricular tachycardia	0	0.2	0.3

Table 3. Incidence of selected serious, including fatal, cardiac adverse events form phase III one-year trials.[1]

Cardiovascular Event	**Placebo-controlled**		**Active-controlled**	
	Tiotropium N=550	**Placebo** N=371	**Tiotropium** N=356	**Ipratropium** N=179
	%	**%**	**%**	**%**
Serious				
Arrhythmia	0.2	0	0	0
Angina pectoris	0.4	0.3	0.8	1.7
Angina pectoris, aggravated	0.2	0	0	0
Atrial fibrillation	0.4	0.3	0	1.1
Cardiac arrest	0.2	0	0	0
Cardiac failure	0.7	0.8	0	0.6
Cardiac failure, right	0	0	0.3	0
Coronary artery disorder	0.7	0.8	0	0
Myocardial infarction	0.5	0.3	0.8	0
Tachycardia	0.2	0	0	0
Supraventricular tachycardia	0.2	0	0	0
Fatal				
Arrhythmia	0.2	0	0	0
Cardiac arrest	0.2	0	0	0
Cardiac failure	0.2	0.3	0	0
Coronary artery disorder	0.2	0.3	0	0
Myocardial infarction	0.2	0	0.8	0

Table 4. Incidence of selected serious, including fatal, cardiac adverse events form phase III six-month trials.[2]

Cardiovascular Event	**Tiotropium** N=402	**Salmeterol** N=405	**Placebo** N=400
	%	**%**	**%**
Serious			
Angina pectoris	0.2	0	0.3
Angina pectoris, aggravated	0	0.5	0
Cardiac arrest	0	0	0.5
Cardiac failure	0	1.5	0.5
Cardiac failure, left	0	0.2	0
Coronary artery disorder	0	0.2	0
Myocardial infarction	0.2	0.5	0.8
Supraventricular tachycardia	0.2	0.2	0
Ventricular tachycardia	0	0.2	0.3
Fatal			
Cardiac arrest	0	0	0.5
Cardiac failure	0	0.2	0

Systemically administered anticholinergic medications may alter heart rate and rhythm.[3] SPIRIVA is a long-acting antimuscarinic agent, often referred to as an anticholinergic medication. Administered by inhalation, SPIRIVA binds to the muscarinic receptors in the bronchial smooth musculature and inhibit the cholinergic (bronchoconstrictive) effects of acetylcholine, a neurotransmitter released from parasympathetic nerve endings. Resulting bronchodilation after administration of SPIRIVA is a site-specific effect, not a systemic one, and it is expected from the chemical structure of the compound (quaternary ammonium compound) that SPIRIVA is poorly absorbed from the gastrointestinal tract (data on file, P).

To ascertain whether cardiac effects could be detected following inhalation of SPIRIVA, electrocardiographic (ECG) evaluations were part of the safety monitoring throughout the clinical development program. ECG and two-minute rhythm strip data were collected as part of the four-week, multi-center, randomized, double-blind, placebo-controlled study that evaluated the dose-response characteristics of SPIRIVA.[4] Patients received either placebo (n=35) or 4.5 mcg (n=34), 9 mcg (n=33), 18 mcg (n=33), or 36 mcg (n=34) of tiotropium once daily. A 12-lead ECG and a two-minute rhythm strip were performed prior to drug administration and at one, three and five hours post drug administration at the randomization visit and after one, two and four weeks of treatment . The fifteen ECG tracings and rhythm strips which were done post drug were compared to the baseline tracing and rhythm strip performed just prior to the first administration of study drug. Any changes seen were changes normally associated among patients with COPD and no differences were noted between placebo and the active treatment groups and, as expected for an anticholinergic, there were no effects observed indicating an increase in QT interval.

Twenty-four hour Holter monitor data were collected as part of the six-week, multi-center, double-blind, placebo-controlled (n=31) study of SPIRIVA 18 mcg inhaled once-daily in the morning (AM, n=37) or evening (PM, n=35) in patients with COPD.[5] Holter studies were performed prior to the first dose and following six weeks of treatment. Patients remained in the clinic for the duration of the Holter studies. None of the groups showed any substantial difference in heart rate and no conduction problems were observed. Additionally, SPIRIVA was not associated with abnormal supraventricular rhythm disorders and no incidences of atrial flutter or fibrillation were observed.[6]
In the one-year placebo (n= 921) and one-year ipratropium-controlled (n=535) trials 12- lead ECGs were performed at baseline and every 90 days for the duration of the trials.[7,8] During the six-month salmeterol and placebo controlled

trials (n=1207) ECGs were performed at baseline and at the conclusion of the trials.[9] ECG evaluations did not detect any imbalances with regard to atrial fibrillation and supraventricular tachycardia after inhalation of SPIRIVA 18mcg once daily.

In a multicenter, randomized, double-blind exercise tolerance trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30-60msec was higher in the SPIRIVA group as compared with placebo.[10] This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500msec. Other clinical studies with SPIRIVA did not detect an effect of the drug on QTc intervals.

A prospective 12 week, parallel group, double-blind, randomized, placebo-controlled study involving 196 patients with COPD (100 treated with tiotropium and 96 with placebo) assessed efficacy of SPIRIVA measured by FEV_1 and assessed cardiac safety by measuring 12 lead and Holter ECG monitoring.[11] The safety results of this study conclude that tiotropium was not associated with ECG changes in heart rate, rhythm, conduction, or QT intervals (including the proportion of patients with changes between 30 – 60 msec) based on results from 12-lead and 24-hour Holter monitoring.

During UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium), which was a four-year randomized, double-blind, placebo-controlled, parallel group clinical trial involving thirty-seven countries, adverse events were collected at each study visit and patient safety was closely followed by an independent Data Safety Monitoring Board. The purpose of the UPLIFT trial was to determine whether treatment with SPIRIVA HandiHaler reduces the rate of decline of FEV_1 over time in patients with COPD.[12] Following completion of the screening visit (Visit 1), patients entered a 2- to 4-week screening period, at the end of which those who qualified were randomized to tiotropium or placebo (Visit 2/Day 1). The use of all previously prescribed respiratory medications, other than inhaled anticholinergics, was permitted if the prescriptions had not changed in the six weeks before randomization. There were no restrictions for medications used to treat exacerbations. Also, the pharmacological treatment for smoking cessation was allowed. All consented active smokers were advised by study personnel to discontinue smoking and were offered a smoking cessation program (e.g., counseling sessions, patient education and supportive literature); however, the participation in such a program was voluntary. Patients were seen one month after the initiation of trial treatment (Visit 3), at three months (Visit 4), and every three months thereafter until study completion (four years) or early discontinuation. Following the double-blinded treatment phase, patients received open-label ipratropium for 30 days. The final trial visit occurred 30 days after completion of the blinded treatment. The incidence of adverse events reported in tiotropium and placebo groups were comparable: 92.6% and 92.3%, respectively. The serious adverse events reported by greater than 1% of patients were either of cardiac or respiratory origin and were more frequent in the placebo group (Table 5). Overall, serious adverse events were reported by 51.6% of tiotropium and 50.2% of placebo patients.

Table 5. Serious cardiac adverse events incidence (per 100 pt-yrs) reported by >1% in any treatment group.[12]**

Serious Adverse Event	Relative Risk (Tio/Placebo)	95% CI
Cardiac System Organ Class (SOC)	**0.84**	**0.73, 0.98***
Angina	1.44	0.91, 2.26
Atrial fibrillation	0.95	0.68, 1.33
Cardiac failure	1.25	0.84, 1.87
Cardiac failure congestive	0.59	0.37, 0.96*
Coronary artery disease	0.58	0.33, 1.01
Myocardial infarction	0.71	0.52, 0.99*

**P*<0.05; **excluding lung cancer (multiple different terms)

Summarized in Table 6 are the UPLIFT findings on the incidences of stroke and myocardial infarction.

Table 6. Incidence of myocardial infarction and stroke.[12]

Adverse Event	Tiotropium (N=2986)	Placebo (N=3006)	Risk Ratio	95% CI
	Rate /100 pt-yrs	Rate /100 pt-yrs		
Myocardial Infarction	**0.71**	**0.98**	**0.73**	**0.53,1.00**
Serious	0.69	0.97	0.71	0.52,0.99
Fatal (on treatment-adj.)	0.10	0.09	1.04	0.40,2.69
Stroke	**0.88**	**0.93**	**0.95**	**0.70,1.29**
Serious	0.70	0.73	0.97	0.69,1.37
Fatal (on treatment-adj.)	0.13	0.15	0.85	0.39,1.87

The data collected during the UPLIFT trial shows that treatment with tiotropium was associated with no increased cardiac morbidity risk, no increased stroke, or myocardial infarction risk,

Kesten S, et al. conducted a retrospective safety analysis for tiotropium.[13] Data was pooled on adverse events from **19 randomized, double-blind, placebo-controlled trials** with tiotropium in patients with COPD (17 studies) and asthma (2 studies) using data available as of May 2004. Heterogeneity of incidence rate ratios was examined by trial prior to pooling. Incidence rates of selected adverse events and Maentel-Haenszel incidence rate ratio estimates were computed, and 95% confidence intervals were used for precision of effect estimates. Patients were included in the study until 30 days post-treatment (tiotropium, placebo) or until they had the event of interest, whichever came first. The pooled population included 7,819 patients (4,435 tiotropium; 3,384 placebo), contributing 2,159 person-years of exposure to tiotropium and 1,662 person-years of exposure to placebo. Serious cardiac conditions, such as cardiac arrest (RR, 0.90; 95%CI, 0.26 to 3.15) and myocardial infarction (RR, 0.74; 95%CI, 0.26 to 2.07) did not occur more frequently with tiotropium. The incidence of selected cardiac adverse events is summarized in Table 7 and the occurrence of serious adverse events of cardiac origin is presented in Table 8.

Table 7. Selected cardiac adverse events form 19 pooled-controlled trials. *[13]

Cardiovascular Event	Tiotropium (N=3521)	Placebo (N=2469)	Risk Ratio	95% CI
	Rate /100 pt-yrs	Rate /100 pt-yrs		
Angina	1.19	1.07	1.17	0.57,2.36
Atrial fibrillation	0.60	0.91	0.70	0.30,1.65
Cardiac arrest	0.30	0.41	0.90	0.26,3.15
Ischemia	0.42	0.49	0.74	0.23,2.41
Myocardial Infarction	0.48	0.66	0.74	0.26,2.07
Other arrhythmias†	1.31	0.49	2.71	1.10,6.65
Tachycardia	1.01	0.58	1.68	0.69,4.11
Ventricular failure, right	0.30	0.08	2.38	0.24,23.18
Ventricular failure, left	0.60	1.48	0.46	0.21,1.00

* Data are presented for two or more selected events in patients receiving tiotropium.

†, Other arrhythmias' include terms such as bradycardia, irregular hear beat, and extrasystole but not ventricular tachycardia/fibrillation or atrial fibrillation.

Table 8. Selected serious, including fatal, adverse events form 19 pooled-controlled trials.[13]

Cardiovascular Event	Tiotropium (N=4435)	Placebo (N=3384)	Risk Ratio	95% CI
	Rate /100 pt-yrs	Rate /100 pt-yrs		
Serious				
Angina	0.78	0.90	0.92	0.46,1.87
Atrial fibrillation	0.23	0.90	0.27	0.10,0.77
Cardiac arrest	0.28	0.48	0.68	0.23,1.97
Ischemia	0.51	0.90	0.58	0.26,1.30
Myocardial Infarction	0.74	0.84	0.96	0.46,2.01
Other arrhythmias†,	0.28	0.30	0.92	0.27,3.14
Tachycardia	0.32	0.24	1.16	0.33,4.03
Ventricular failure, left	0.74	1.44	0.59	0.31,1.11
Ventricular failure, right	0.23	0.06	2.77	0.32,24.17
Ventricular failure, left	0.74	1.44	0.59	0.31,1.11
Ventricular tachycardia/ Ventricular fibrillation	0.28	0.30	1.10	0.34,3.60
Fatal	**0.51**	**0.96**	**0.57**	**0.26,1.26**
Cardiac arrest	0.18	0.42	0.50	0.14,1.76
Myocardial Infarction	0.14	0.06	2.65	0.26,27.13
Other arrhythmias†,	0.05	0.06	0.75	0.04,15.74

†, Other arrhythmias' include terms such as bradycardia, irregular hear beat, and extrasystole but not ventricular tachycardia/ fibrillation or atrial fibrillation.

The current integrated clinical trial database includes **30 long-term and short-term randomized, double-blind, placebo-controlled clinical trials** with tiotropium.[12,14] The integrated clinical trial population includes information

on 19,545 patients from 30 clinical trials (10,846 tiotropium; 8,699 placebo), contributing 14,036 person-years of exposure to tiotropium and 11,810 person-years of exposure to placebo. The updated analysis reaffirms the established long-term safety profile for anticholinergics. There were a total of 212 patients with myocardial infarction (RR, 0.78; 95% CI 0.59, 1.02) and 218 patients with stroke (RR, 1.03; 95% CI 0.79, 1.35), irrespective of adverse event seriousness. The results of the 30 pooled clinical trials analysis have not yet been published.

In conclusion, infrequent or rare associations with increases in heart rate may be observed with SPIRIVA. The SPIRIVA package insert states that atrial fibrillation and supraventricular tachycardia were reported with an incidence of <1% during clinical trials as described above. Pooling of adverse event data from pre-approval and post-approval clinical trials increases the precision of effect estimates and is consistent with the present safety profile of tiotropium.

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Combined with Inhaled Corticosteroids

COPD treatment guidelines recommend initial treatment with inhaled bronchodilators. In addition to bronchodilator therapy, inhaled corticosteroids (ICS) are often prescribed in patients with severe and very severe COPD. Tiotropium is a once daily-inhaled anticholinergic for the treatment of COPD that elicits its effect through prolonged M_3-receptor antagonism. Hodder, et al. sought to determine the benefits of tiotropium and ICS combination therapy by retrospectively reviewing two similar six-month double-blind, double-dummy trials during which COPD patients were assigned to tiotropium 18 mcg once daily, salmeterol 50 mcg bid, or placebo.[1] The analysis was based on combining the trials and analyzing patients treated with ICS at the time of randomization separately from those patients who were not receiving concurrent ICS therapy. A detailed description of the two 6-month trials has previously been published by Bruscaco et al. and Donohue et al.[2, 3]

Of 1207 patients who participated in the two 6-month trials, 796 were receiving ICS therapy. Demographics and characteristics of patients in the two groups (ICS users and ICS non-users) were similar. At baseline, the ICS non-users had slightly less airway obstruction and better health status scores than the ICS users. The most commonly used inhaled corticosteroids were fluticasone (41% of ICS users in the tiotropium, 36% in the salmeterol, and 44% in the placebo arm, median daily dose of 1000 mcg), budesonide (33% of ICS users in the tiotropium, 35% in the salmeterol, and 29% in the placebo group, median daily dose of 800 mcg), and beclamethasone (23% of ICS users in the tiotropium, 25% in the salmeterol, and 22% in the placebo arm, median daily dose of 1000 mcg). Of 168 ICS users who withdrew from the studies, a significantly smaller number withdrew from the tiotropium and the salmeterol arms compared with the placebo arm (17%, 19%, and 27%, respectively, $P<0.05$). Also, significantly fewer of the 68 ICS non-users who prematurely discontinued trial participation were from the tiotropium group compared with the placebo arm (11% versus 23%, $P<0.05$). The difference between the salmeterol and placebo groups was not statistically significant. The differences in the incidence of adverse events leading to patient discontinuation were not statistically significant between the ICS users and non-users: tiotropium: 9% versus 4%, salmeterol: 16% versus 13%, and placebo: 18% versus 15%, respectively. The most common reason for patient withdrawal among ICS users and non-users was worsening of COPD: tiotropium: 6% versus 3%, salmeterol: 12% versus 6%, and placebo: 12% versus 10%, respectively.

Mean FEV_1 in the ICS user subgroup was 1.08 liters (L) in patients randomized to tiotropium (n=259), 1.03L in the salmeterol arm (n=278), and 1.09L in the placebo group (n=259). Mean FEV_1 values in the ICS non-user subgroup were 1.18L in the tiotropium arm (n=135), 1.14L in the salmeterol group (n=120), and 1.07L in the placebo arm (n=135). After 169 days, morning pre-dose (trough) improvement in FEV_1 above placebo among the ICS users was 110±20 ml for tiotropium and 80±20 ml for salmeterol ($P=0.11$ for tiotropium versus salmeterol, $P<0.001$ for either active treatment versus placebo). Trough improvement in FVC above placebo was 220±40 ml for tiotropium and 130±40 ml for salmeterol ($P<0.05$ tiotropium versus salmeterol, $P<0.001$ either active treatment versus placebo). The spirometric findings were similar in the ICS non-user subgroup; however, because of the smaller sample size (n=360) and insufficient power, the statistical significance of the difference between the tiotropium and the salmeterol arm could not be determined.

In the ICS user subgroup, compared with placebo, mean transition dyspnea index (TDI) focal score after 169 days was higher in the tiotropium (1.03±0.4 units, $P<0.01$) than the salmeterol (0.57±0.4 units, not statistically significant) arm. While the difference in the TDI focal score between the tiotropium and salmeterol groups was not statistically significant at 169-day timepoint, only patients in the tiotropium arm achieved the minimal clinically important difference of 1 unit. In contrast, in patients not concurrently treated with ICS, the mean TDI focal score after 169 days reached the clinically important difference of one unit in both the tiotropium and salmeterol arms; however, this finding was statistically significant versus placebo only in the tiotropium group.

In addition, the percent of patients who experienced at least 1 exacerbation was lower in both tiotropium and salmeterol arms compared with placebo (40%, 40%, 45%, respectively); however, the differences did not reach statistical significance. The findings related to the reduction in the number of exacerbations in the ICS non-user subgroup were similar. Lastly, among the ICS users, changes in SGRQ total score relative to placebo were -3.27±1.2

for the tiotropium (P<0.01) and -1.12±1.2 for the salmeterol (P>0.05) groups. The difference between the tiotropium and salmeterol arms was not statistically significant. However, when compared to baseline, the change in SGRQ score reached the accepted minimally important clinical difference of at least 4 units only in the ICS users receiving tiotropium. Among patients not receiving ICS, changes in SGRQ total score compared with placebo were -2.05±1.7 for tiotropium and -1.66±1.8 for salmeterol. Neither finding reached statistical significance.

In summary, the post-hoc analysis by Hodder et al of COPD patients receiving concomitant inhaled steroids during two 6-month clinical trials demonstrates that tiotropium provided benefits over salmeterol in lung function, dyspnea, and quality of life.

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Formoterol Versus and in Combination with SPIRIVA

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines, regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators and is recommended as maintenance therapy. The guidelines further state that "combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator". Long-acting inhaled bronchodilators now include two classes of medications: long-acting β-adrenergic agonists and the only currently available long-acting anticholinergic, SPIRIVA HandiHaler (tiotropium bromide inhalation powder). Both classes are considered by the GOLD Guidelines to be first-line maintenance medications for COPD. Anticholinergic inhalation therapy has a prominent place in many consensus statements.[1,2]

Studies have suggested that the once-daily anticholinergic tiotropium may be considered the bronchodilator of choice for the maintenance therapy of COPD. Cazzola et al. [3] designed a double-blind, double-dummy, cross-over, randomized pilot study to compare the acute bronchodilator efficacy of a single dose of formoterol 12mcg with that of tiotropium 18mcg in 20 patients with stable COPD. The acute effects of adding tiotropium 18mcg to formoterol 12mcg were explored in this study to determine the potential for additive bronchodilation. Serial measurements of FEV_1 were performed over 24 hours. Formoterol, alone or in combination with tiotropium, produced a significantly faster onset of action and showed a trend for a greater maximum bronchodilation than tiotropium alone. At 24 hours, mean FEV_1 continued to be significantly higher than pre-dosing value following tiotropium and formoterol plus tiotropium. However, the study is limited as additional bronchodilator effects with tiotropium occur beyond the first dose. Pharmacodynamic steady state is attained within eight days. Single dose studies for maintenance treatment need to be interpreted with caution.

Once daily tiotropium 18mcg inhaled via the HandiHaler, twice daily formoterol 12mcg inhaled as dry powder, and the once daily free combination of both drugs (tiotropium plus formoterol) were compared by van Noord et al.[4] using a 3-way, double-blind, crossover design of 6-week treatment periods. Mean baseline FEV_1 of the 74 randomized patients was 1.05L (32% of predicted), mean age was 64.8 years. Bronchodilator efficacy (FEV_1, FVC) was assessed at the end of each 6-week treatment period for a 24-hour observation period. Tiotropium was superior to formoterol during the day for FEV_1 and FVC average (0-12 hours) as well as trough response; no difference was observed in FEV_1 and FVC average (12-24 hours). The free combination of both drugs taken once daily appeared to be superior to the single drugs for most of the endpoints, except for FEV_1 and FVC trough response, and average FVC (12-24 hours) in COPD patients with moderate to severe airflow obstruction.

Rabe KF et al.[5] conducted a 6-week, multicenter, randomized, double-blind, quadruple-dummy, parallel group study to compare efficacy and safety of tiotropium 18mcg once daily plus formoterol 12mcg twice daily (n=304) to salmeterol 50mcg twice daily plus fluticasone 500mcg twice daily (n=301) in patients with COPD. Co-primary endpoints were FEV_1 area under the curve from 0 to 12 hours (FEV_1 $AUC_{0\text{-}12h}$) and peak FEV_1 at 6 weeks. In addition to FVC $AUC_{0\text{-}12h}$ after 6 weeks of treatment, morning pre-dose FEV_1 and FVC at 3 and 6 weeks were the secondary efficacy endpoints. The following spirometric criteria were inclusionary: Visit 1 post-bronchodilator FEV_1 <80% of predicted and FEV1/FVC ratio <70% as well as Visit 2 pre-bronchodilator FEV_1 ≤65% of predicted. In addition, patients had to be 40 years of age or older and have a smoking history of more than 10 pack-years. Treatment with inhaled corticosteroids (ICS) within two months of screening and use of oral steroids within six weeks of screening was exclusionary. Prior to randomization, patients entered a two to 4-week run-in period the duration of which was related to the pre-screening use of tiotropium (non-users entered a 2-week run-in period and users, a 4-week one). The use of ICS, oral steroids (except for exacerbation management), tiotropium, β-agonists and anticholinergics other than the supplied rescue medication, and once-a-day theopylline preparations was not permitted during the entire trial duration. Pre-dose spirometric parameters were collected at 3 weeks. After 6 weeks, a 12-hour pulmonary function testing was performed. Efficacy evaluation (intent-to-treat) comprised 592 patients: 297 in the tiotropium plus formoterol arm and 295 in the salmeterol plus fluticasone group. The treatment groups were comparable with respect to demographic characteristics (approximately 70% male, mean age: 62±9 years, median smoking history: 40 pack-years, and median duration of COPD: 75 months) as well as pulmonary function (mean post-bronchodilator FEV_1 approximately 55% of predicted mean post-bronchodilator FEV_1/FVC ratio

approximately 52% of predicted). At the end of the trial, tiotropium plus formoterol was significantly superior in FEV_1 AUC_{0-12} (78mL, P=0.0006) and peak FEV_1 (103mL, p<0.0001) to salmeterol plus fluticasone. Also, tiotropium plus formoterol was significantly superior with respect to FVC AUC_{0-12h} 173 mL, P<0.0001 and peak FVC (214mL, P<0.0001). Both pre-dose FEV_1 (P>0.05) and FVC (79mL, P<0.05) were higher in the tiotropium plus formoterol arm. 3-week spirometry results were similar. Overall, both treatments were well-tolerated. Adverse events were reported by 28.5% of patients in the tiotropium plus formoterol group and by 27.8% of patients randomized to the fluticasone plus salmeterol arm. In each treatment group, COPD exacerbation and pharyngitis were reported at the rate of ≥3%, four patients reported dry mouth, six patients experienced serious adverse events, and one patient died (myocardial infarction, bronchial cancer).

During a 12-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter study in current or ex-smoker COPD patients aged ≥ 40 years, Tashkin and Varghese investigated whether the therapeutic effect of treatment with formoterol in combination with tiotropium was greater than the effect of treatment with tiotropium alone.[6] Patients were randomized to receive either formoterol 12mcg twice daily plus tiotropium 18mcg once daily or tiotropium 18mcg once daily in combination with placebo. The primary efficacy endpoint was the change from baseline in the normalized area under the curve (AUC) for FEV_1 measured 0 to 4 hours after the morning dose (FEV_1 AUC_{0-4h}) following 12-weeks of treatment. Comparisons of trough FEV_1 and FVC (average of values 10 and 30 minutes pre-dose) and onset of change in FEV_1 following the first dose were among the secondary efficacy endpoints. The normalized FEV_1 AUC_{0-4h} was significantly increased in the formoterol plus tiotropium treatment arm (n=116) compared with tiotropium alone group (n=124) at all time points. Mean treatment differences were both statistically and clinically significant (>100ml change) at 4, 8, and 12 weeks. At the end of the trial, increases from baseline in trough FEV_1 and FVC observed in the formoterol plus tiotropium group (n=121) were significantly greater than those in the tiotropium monotherapy arm (n=129). The mean differences between the two treatment arms were 80ml for trough FEV_1 and 160ml for trough FVC (both P=0.004). In terms of FEV_1 5 minutes post-dose, the increase was significantly greater in the formoterol plus tiotropium group compared with tiotropium alone (180ml versus 40ml, respectively; P<0.001). Both treatments were found to be well tolerated.

Another comparison trial evaluated bronchodilatory effects of formoterol, tiotropium, and formoterol plus tiotropium versus placebo measured as 2 h post-dose FEV_1 at the end of the 24-week treatment period.[7] Also, information regarding different levels of COPD exacerbation, from COPD-related "bad days", defined as days with at least 2 out of 5 symptoms in the patient diary recorded with a score of 2 or more, to COPD-related hospitalizations was collected.[8] After a 14-day run-in period, 847 patients with stable COPD (FEV_1<70% predicted, FEV_1/FVC<70%) were randomized to one of the following treatment groups: (1) formoterol 10mcg twice daily via Certihaler™ Multi-Dose Dry Powder Inhaler (n=210), (2) tiotropium 18mcg daily via the Handihaler® (n=221), (3) combination of tiotropium and formoterol (n=207), or (4) placebo (n=209). Tiotropium was administered in an open-label fashion while the administration of formoterol was double-blinded. Compared with placebo, formoterol demonstrated rapid onset of action as measured by increase in FEV_1 5 min post dose on the first treatment day (100ml, P<0.001). After 24 weeks, combination therapy was superior to tiotropium alone (80ml difference in FEV_1 at 5 min post dose, P=0.013). In terms of 2 h post dose FEV_1 values, at the end of the 24-week treatment period and compared with placebo, both formoterol and tiotropium showed statistically significant bronchodilation (170ml and 180ml increase, respectively, both P<0.001). The difference between formoterol and tiotropium treatment arms was not statistically significant (p=0.855). Combination treatment provided greater bronchodilatory effect compared with placebo (2 h post dose FEV_1 increased by 240ml, P<0.001); however, the difference between the combination treatment and either active monotherapy arm did not reach statistical significance (P≤0.066). Compared with placebo, the active treatment arms decreased the incidence of COPD-related "bad days" by approximately 8% (P≤0.004). The percentage of patients with COPD exacerbations warranting additional treatment was the lowest in the combination treatment arm (6% versus 8% in the formoterol, 10% in the tiotropium, and 14% in the placebo treatment arm). The difference versus placebo was statistically significant for formoterol and combination therapy. The differences in the percentage of patients experiencing exacerbations resulting in hospitalization were not statistically significant in any of the treatment arms (formoterol 0.5%, tiotropium 2.3%, combination therapy 1.4%, and placebo arm 1.4% of patients). All four treatments appeared to be generally safe and well tolerated.

Tashkin et al.[9] sought to compare safety and efficacy of nebulized formoterol fumarate (Perforomist, 20mcg/2ml) twice daily with nebulized placebo twice daily added to daily treatment with tiotropium 18mcg (FFIS/TIO versus PLA/TIO) during a 6-week, randomized, double-blind, placebo controlled, parallel group study. Prior to randomization, patients received 18mcg tiotropium bromide daily for 7 to 14 days (run-in period). PARI LC® Plus jet nebulizer with PARI PRONEB® compressor was used to administered formoterol/placebo and tiotropium was delivered via the HandiHaler® inhalation device. Tiotropium was administered before FFIS or PLA. The primary efficacy endpoint was the standardized area under the curve for FEV_1 over 3h (FEV_1 AUC_{0-3}) at the end of trial. Trial participants were at least 40-years-old, current or ex-smokers diagnosed with COPD. The spirometeric inclusion criteria at screening were post-bronchodilator FEV_1 ≥25% and <65% of predicted and FEV_1/FVC ratio of <0.70. At the randomization visit, pre-dose FEV_1 <70% of predicted was required. During trial participation (both run-in and double-blind period), the use of long-acting bronchodilators including anticholinergics, theophylline, nedocromil, or cromolyn sodium was not permitted. Albuterol was provided as a rescue medication. At randomization and at the end of trial, ECGs were performed pre-and post-dose, St. George's Respiratory Questionnaire (SGRQ) was administered, and spirometry was preformed at 5 and 30 min pre-dose as well as at 5, 30 minutes, 1, 2, and 3 hours post-dose. A baseline dyspnea index was administered at randomization and a transitional dyspnea index (TDI) at the end of trial. Spirometric measurements, safety assessments, and collection of diary cards with self-report of study and rescue medication use and symptom scores occurred at 1, 3, and 6 weeks. In each treatment arm (FFIS/TIO n=67 and PLA/TIO n=63), the mean age of patients was approximately 65 and about 70% of participants were male. There were fewer current smokers in the PLA/TIO group (32%) compared with the FFIS/TIO group (42%). In general, the two groups were balanced in terms of demographic characteristics and pulmonary function. The mean baseline pre-dose FEV_1 was 1.19L (38.4% of predicted). The standardized absolute FEV_1 AUC_{0-3} measured following the first dose on Day 1 was significantly higher in the FFIS/TIO compared to PLA/TIO, 1.47L and 1.33L, respectively (P<0.0001). Similar improvement in FEV_1 AUC_{0-3} was also observed after 6 weeks of treatment (FFIS/TIO group: 1.52L and PLA/TIO group: 1.34L, P<0.0001). FVC AUC_{0-3} measured post-dose on Day 1 and after week 6 was also found to be significantly greater in the FFIS/TIO group than in the PLA/TIO arm (P<0.0001). An improvement in lung function 5 minutes post dose on Day 1 and after 6 weeks was noted in the FFIS/TIO but not the PLA/TIO group. Compared with PLA/TIO group, the use of rescue albuterol was also reduced in the FFIS/TIO arm starting during Week 1 (at 6 weeks, P≤0.0001). From Week 3 to Week 6, total respiratory symptom scores were significantly improved and fewer respiratory symptoms (shortness of breath, chest tightness, night-time awakenings) were reported in the FFIS/TIO treatment arm compared with the PLA/TIO group. After 6 weeks of treatment, the mean dyspnea scores were also significantly improved in the FFIS/TIO compared with PLA/TIO arm. The SGRQ scores did not change significantly throughout the treatment period. However, the decrease in the 6-week versus baseline SGRQ scores reached clinical significance (>4 units) in the FFIS/TIO group (P=0.04). A total of 16 subjects discontinued the study, 8 from each treatment arm. Fewer patients in the FFIS/TIO group reported at least one adverse event compared with the PLA/TIO group (24 versus 40% of participants). Of these adverse events 13% and 6% respectively were determined to be drug-related. The most commonly reported adverse events were COPD exacerbation, cough, pulmonary congestion, nasopharyngitis, diarrhea, vomiting, and insomnia. Lab findings were within normal limits with the exception of one patient in the FFIS/TIO arm who had decreased serum potassium. While two patients from the FFIS/TIO and one from PLA/TIO group had maximum changes in QTcB interval ≥60ms, the changes in PR, RR, and QRS intervals were insignificant.

The body of clinical evidence supporting the concomitant use of anticholinergics and long-acting β-agonists is growing. Safety concerns are not anticipated when adding SPIRIVA to a long-acting β -agonist beyond those described with the individual monosubstances.

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INSPIRE Trial

INSPIRE (**I**nvestigating **N**ew **S**tandards for **P**rophylaxis **i**n **R**educing **E**xacerbations) was a 2-year multicenter, randomized, double-blind, double-dummy controlled trial. Of note, tiotropium capsules had printing on the capsule, which could be identified as tiotropium while the placebo capsules did not have the printing on the capsule. As a result, the tiotropium could be identified from the placebo and conclusions could be drawn regarding the contents of the Diskus (active versus inactive). Before randomization, patients discontinued all existing COPD maintenance medications and received oral prednisolone 30 mg/day along with inhaled salmeterol 50 mcg twice daily for 2 weeks (run-in period) to standardize their clinical condition. Qualifying patients were randomized to inhaled salmeterol 50 mcg plus fluticasone propionate 500 mcg combination (SFC) twice daily by Diskus or tiotropium bromide 18 mcg once daily via HandiHaler. After randomization, in addition to study medication, patients were allowed short-acting inhaled beta-agonists as rescue therapy and standardized short courses of oral systemic corticosteroids and/or antibiotics as needed for treatment of COPD exacerbations. Details of any COPD exacerbations, unscheduled health care visits, and adverse events were recorded at 2, 8, and every 12 weeks thereafter. Post-dose FEV_1 and other respiratory parameters were measured at weeks 2 and 8, and every 24 weeks thereafter with St. George's Respiratory Questionnaire (SGRQ) collected at weeks 32, 56, 80, and 104.

The inclusion criteria were as follows: patients aged 40 to 80 years with a smoking history of 10 or more pack-years, a clinical history of COPD exacerbations, a post-bronchodilator FEV_1 of less than 50% predicted, reversibility to 400 mcg salbutamol 10% or less of predicted FEV_1, and a score of 2 or more on the Modified Medical Research Council dyspnea scale. Patients with any respiratory disorder other than COPD or who required daily long term oxygen therapy (>12 h/d) were excluded from the trial.

The primary efficacy endpoint was the rate of health care utilization (HCU) exacerbations. These were defined as requiring treatment with oral corticosteroids and/or antibiotics or requiring hospitalization. Secondary endpoints included health status measured using SGRQ, post-dose FEV_1, which was measured 2 h after inhalation of study medication, and withdrawal rate from the trial. All-cause mortality was considered an efficacy and safety endpoint. To assess safety, all adverse events together with an oropharyngeal examination for evidence of candidiasis and inspection of the volar aspect of the forearm for spontaneous bruises were documented. Additionally, at weeks 0, 56, and 104, electrocardiograms were performed.

Of 1,499 patients, 1,323 were randomized and used in the intent-to-treat analysis. No difference was found between estimated overall rates of exacerbations (SFC, 1.28/yr; tiotropium, 1.32/yr; P = 0.656). Similarly, no difference was observed between the study arms for the occurrence of exacerbations requiring hospitalization (16% for SFC arm and 13% for tiotropium arm, P = 0.085). Exacerbations requiring antibiotics occurred less frequently in patients treated with tiotropium (tiotropium, 0.82/yr; SFC 0.97/yr; P = 0.028) whereas those requiring systemic corticosteroids were less frequent in the SFC arm (SFC, 0.69/yr; tiotropium, 0.85/yr; P = 0.039).

Mean SGRQ total score values at screening were 50.3 units for the SFC and 52.3 for the tiotropium treatment groups and improved after the treatment during the run-in period to 48.0 and 48.2 units at baseline, respectively. The total SGRQ score was statistically significantly higher in the tiotropium group than the SFC group at Weeks 32, 56, 80, and 104; however, this statistical difference did not reach the minimum clinically important 4-unit difference between the treatment arms. At Week 104, the percentage of patients who achieved a clinically important improvement in SGRQ score was greater in the SFC than the tiotropium group (32% and 27%, respectively; P = 0.021). No difference in adjusted mean FEV_1 post-dose between the treatments was demonstrated at the completion of the trial.

The INSPIRE investigators reported that mortality was significantly lower in the SFC treatment group; 21 (3%) of SFC patients and 38 (6%) of those in the tiotropium group died (P = 0.032) during the study period. It is important to note that INSPIRE was powered for the efficacy endpoint but was not designed as a mortality trial. There was no independent adjudication of individual fatal cases and patients who did not complete the study were not followed up. No definitive conclusions, therefore, can be drawn from the apparent differences between the two treatment arms.

Overall safety findings, including fatal events, were consistent with a population of patients with severe and very severe COPD. The frequency of adverse events was similar in the two treatment arms with 66% of SFC patients and 62% of those receiving tiotropium reporting some adverse event. COPD exacerbations were reported most frequently. The incidence of serious adverse events was lower with tiotropium. SAEs were reported during treatment by 30% of SFC-treated and 24% of tiotropium-treated patients. Fatal events were reported in 38 (6%) patients in the tiotropium group and in 21 (3%) patients in the SFC group. The rate of pneumonia was higher in the SFC group (8 versus 4% in tiotropium arm) and the hazard ratio for time to reported pneumonia was 1.94 (P = 0.008) for SFC compared with tiotropium over the 2 years. The incidence of reported pneumonias that overlapped with an exacerbation treated with antibiotics was 55% in the SFC group and 48% in the tiotropium group (i.e., the other episodes were not given antibiotic treatment despite the report of pneumonia). A total of 14 patients were withdrawn from the study due to pneumonia (9 in SFC and 5 in tiotropium group). Other adverse events of interest (e.g., fractures, bruising, candidiasis) were infrequent.

Patients randomized to tiotropium were significantly more likely to withdraw from the study than those randomized to SFC as evidenced by the estimated probability of withdrawing before Week 104 of 41.7% in the tiotropium group and 34.5% in the SFC group (hazard ratio of 1.29, P = 0.005). The reported withdrawal rates in the SFC and tiotropium groups are shown in the table below. The details regarding the consent withdrawal have not been disclosed.

	SFC Arm – n (%)	***Tiotropium Arm – n (%)***
Adverse event	67 (10.2)	66 (9.9)
Consent withdrawal	61 (9.3)	82 (12.3)
Loss to follow-up	15 (2.3)	13 (2.0)
Protocol violation	7 (1.1)	8 (1.2)
Failure to meet entry criteria	0	3 (0.5)
COPD exacerbation	37 (5.6)	51 (7.7)
Lack of efficacy	32 (4.9)	38 (5.7)
Other	13 (2.0)	17 (2.6)
Missing	0	1 (0.2)
Total	232 (35.3)	279 (42.0)

SPIRIVA has a well established efficacy and safety profile in patients with COPD.[2] This has been demonstrated by an extensive clinical trial program including over 10,000 patients, and almost eight million patients have benefited from SPIRIVA since it was first introduced in 2002.[3] In addition, the four-year, landmark study **U**nderstanding **P**otential **L**ong-term **I**mpacts on **F**unction with **T**iotropium (UPLIFT) will report data in 2008.

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Salmeterol Plus Fluticasone Combined with SPIRIVA

A publication in the Annals of Internal Medicine reviewed the results of the Canadian OPTIMAL trial where the combination of tiotropium with salmeterol or fluticasone-salmeterol was compared to tiotropium alone in improving moderate to severe COPD. The study by Aaron SD et al. was a randomized, double-blind, placebo-controlled trial conducted from Oct 2003 to January 2006 at 27 academic and community medical centers in Canada. 449 patients with moderate to severe COPD participated receiving 1 year of treatment with tiotropium with placebo, tiotropium with salmeterol, or tiotropium with fluticasone-salmeterol. The primary endpoint was the proportion of patients who experience a COPD exacerbation that required treatment with systemic steroids or antibiotics.[1]

The proportion of patients in the group that received tiotropium plus placebo who experienced an exacerbation (62.8%) did not differ from that in the tiotropium plus salmeterol group (64.8%; difference, -2 percentage points[95% CI, -12.8 to 8.8 percentage points] or the tiotropium plus fluticasone-salmeterol group (60.0%; difference, 2.8 percentage points [CI, -8.2 to13.8 percentage points]. In sensitivity analyses, the point estimates and 95% confidence bounds shifted in the direction favoring tiotropium plus salmeterol and tiotropium plus fluticasone-salmeterol. In analyses of secondary endpoints, tiotropium plus fluticasone-salmeterol improved lung function (p=0.049) and disease-specific quality of life (p=0.01) and reduced the number of hospitalizations for COPD exacerbations and all-cause hospitalizations compared with tiotropium. In contrast, tiotropium plus salmeterol did not statistically improve lung function or hospitalization rates compared with tiotropium plus placebo.[1]

A limitation of the study was that more than 40% of patients who received tiotropium and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label inhaled steroids or long-acting beta-agonists.[1]

Adding fluticasone-salmeterol to tiotropium therapy did not statistically influence the incidence of COPD exacerbations but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD.[1]

A pilot, double-blind, double-dummy, randomized, parallel group design trial to assess feasibility of adding an inhaled corticosteroid to two long-acting bronchodilators was conducted by Cazzola et al.[2] Ninety patients with well-controlled COPD were enrolled into the trial. Inclusion criteria required age of 50 or older, current smoking status or a smoking history of at least 20 pack-years, a baseline FEV_1 of less than 50% predicted, and a post-bronchodilator $FEV_1/FVC < 70\%$ predicted. Exclusion criteria were as follows: current evidence of asthma as primary diagnosis, unstable respiratory disease requiring oral/parenteral corticosteroid within 4 weeks prior to beginning the trial, upper or lower respiratory tract infection within 4 weeks of the screening visit, unstable angina or unstable arrhythmias, concurrent use of medications that affect COPD, and evidence of alcohol abuse. At the end of the 2-week run-in period, during which pre-trial COPD treatments (with the exception of stable theophylline regimens) were stopped, patients were randomized into one of three treatment arms: (1) fluticasone/salmeterol 500/50 μg combination (FSC), (2) tiotropium 18 μg, or (3) FSC 500/50 μg + tiotropium 18 μg.

After 4, 8, and 12 weeks of therapy, patients returned to the clinic for study visits. Trough FEV_1 and FVC values were measured, changes in the perception of dyspnea were assessed (through use of bipolar visual anagogic scale [VAS]), and use of supplemental salbutamol was monitored. The primary efficacy measure was the mean change from baseline in pre-dose FEV_1 after 3-month treatment. Secondary efficacy endpoints included change from baseline in VAS score and the use of supplemental salbutamol.

Eighty-one patients completed the trial (26 in the FSC arm, 26 in the tiotropium arm, and 29 in the FCS + tiotropium arm). At baseline, there were no significant ($p<0.05$) spirometric differences between the three treatment groups. After 1 month, significant increases in trough FEV_1 values were observed in all three groups (117mL in FSC, 74mL in the tiotropium, and 115mL in the FSC + tiotropium arm). The difference between the FEV_1 improvements in the FSC and tiotropium arms and that between the tiotropium and the FSC + tiotropium arms was statistically significant, whereas the difference between the FSC and the FSC + tiotropium arms was not. At the end of the trial,

FEV_1 values were improved above baseline by 140mL, 141mL, and 186mL in the FSC, the tiotropium, and the FSC + tiotropium arm, respectively. All three increases reached statistical significance. The difference between the improvements in the FSC and tiotropium groups was not statistically significant; however, the differences between the improvements in the FSC + tiotropium and the mono-component arms were statistically significant. At the end of the treatment, tiotropium and FSC + tiotropium arms showed greater improvements in dyspnea (measured by VAS score) than those observed in the FSC arm. All of the improvements were statistically significant when compared to the baseline, but not significant when compared to one another. The daily use of salbutamol was significantly lower during the treatment period than the 2-week run-in, but similarly to the VAS scores, the differences between the three treatment groups were not statistically significant. Nonetheless, FSC + tiotropium group required fewer puffs of salbutamol than the mono-component groups. The investigators noted that the trial was likely underpowered to detect statistically significant differences in the VAS scores and the use of salbutamol between the three treatment groups. They pointed out, however, that a trial in a larger patient population would potentially find these differences to be statistically significant.

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Salmeterol Plus Fluticasone Versus SPIRIVA

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines, bronchodilators are central in the symptomatic management of COPD and are considered the first-line maintenance therapy for various stages of COPD.[1] In patients with moderate-to-very severe COPD whose dyspnea during daily activities is not relieved despite treatment with as-needed short-acting bronchodilators, adding regular treatment with a long-acting inhaled bronchodilator is recommended.[1] Long-acting inhaled bronchodilators now include two classes of medications: long-acting beta-adrenergic agonists (salmeterol and formoterol) and a long-acting anticholinergic, SPIRIVA HandiHaler (tiotropium bromide inhalation powder). [1] In addition, the GOLD Guidelines recommend regular treatment with inhaled corticosteroids in addition to long-acting bronchodilator (sympathomimetic or anticholinergic) in patients with severe-to-very severe COPD and a history of repeated exacerbations.[1]

A pilot, double-blind, double-dummy, randomized, parallel group design trial to assess feasibility of adding an inhaled corticosteroid to two long-acting bronchodilators was conducted by Cazzola et al.[2] Ninety patients with well-controlled COPD were enrolled into the trial. Inclusion criteria required age of 50 or older, current smoking status or a smoking history of at least 20 pack-years, a baseline FEV_1 of less than 50% predicted, and a post-bronchodilator $FEV_1/FVC < 70\%$ predicted. Exclusion criteria were as follows: current evidence of asthma as primary diagnosis, unstable respiratory disease requiring oral/parenteral corticosteroid within 4 weeks prior to beginning the trial, upper or lower respiratory tract infection within 4 weeks of the screening visit, unstable angina or unstable arrhythmias, concurrent use of medications that affect COPD, and evidence of alcohol abuse. At the end of the 2-week run-in period, during which pre-trial COPD treatments (with the exception of stable theophylline regimens) were stopped, patients were randomized into one of three treatment arms: (1) fluticasone/salmeterol 500/50mcg combination (FSC) via Diskus twice-daily plus placebo via HandiHaler once daily, (2) tiotropium 18mcg via HandiHaler once-daily plus placebo Diskus twice-daily, or (3) FSC 500/50mcg via Diskus twice-daily + tiotropium 18mcg via HandiHaler once-daily.

After 4, 8, and 12 weeks of therapy, patients returned to the clinic for study visits. Trough FEV_1 and FVC values were measured, changes in the perception of dyspnea were assessed (through use of bipolar visual anagogic scale [VAS]), and use of supplemental salbutamol was monitored. The primary efficacy measure was the mean change from baseline in pre-dose FEV_1 after 3-month treatment. Secondary efficacy endpoints included change from baseline in VAS score and the use of supplemental salbutamol.

Eighty-one patients completed the trial (26 in the FSC arm, 26 in the tiotropium arm, and 29 in the FCS + tiotropium arm). At baseline, there were no significant ($p<0.05$) spirometric differences between the three treatment groups. After 1 month, significant increases in trough FEV_1 values were observed in all three groups (117mL in FSC, 74mL in the tiotropium, and 115mL in the FSC + tiotropium arm). The difference between the FEV_1 improvements in the FSC and tiotropium arms and that between the tiotropium and the FSC + tiotropium arms was statistically significant, whereas the difference between the FSC and the FSC + tiotropium arms was not. At the end of the trial, FEV_1 values were improved above baseline by 140mL, 141mL, and 186mL in the FSC, the tiotropium, and the FSC + tiotropium arm, respectively. All three increases reached statistical significance. The difference between the improvements in the FSC and tiotropium groups was not statistically significant; however, the differences between the improvements in the FSC + tiotropium and the mono-component arms were statistically significant. At the end of the treatment, tiotropium and FSC + tiotropium arms showed greater improvements in dyspnea (measured by VAS score) than those observed in the FSC arm. All of the improvements were statistically significant when compared to the baseline, but not significant when compared to one another. The daily use of salbutamol was significantly lower during the treatment period than the 2-week run-in, but similarly to the VAS scores, the differences between the three treatment groups were not statistically significant. Nonetheless, FSC + tiotropium group required fewer puffs of salbutamol than the mono-component groups. The investigators noted that the trial was likely underpowered to detect statistically significant differences in the VAS scores and the use of salbutamol between the three treatment groups. They pointed out, however, that a trial in a larger patient population would potentially find these differences to be statistically significant.

Results of another pilot trial were reported by Bateman et al.[3] It was a 6-week, multicenter, randomized, double-blind, triple-dummy, parallel group, study comparing bronchodilatory effects of once-daily tiotropium versus twice-daily salmeterol plus fluticasone combination. The study was conducted at 12 centers in South Africa. To meet the inclusion criteria, male or female patients had to be at least 40 years-old, have a diagnosis of COPD with post-bronchodilator FEV_1 <80% predicted, FEV_1/FVC <70% predicted at screening, and pre-dose FEV_1 ≤65%predicted at baseline (Day 1), and have smoking history ≥10 pack-years. The following criteria were exclusionary: history of asthma, allergic rhinitis or atopy, blood eosinophil count ≥600/mm^3, respiratory tract infection in the last six weeks, myocardial infraction in the last six months, cardiac arrhythmia requiring drug therapy, heart failure in the past year or pulmonary edema, regular daytime use of oxygen, use of oral or inhaled steroids alone or in combination with a long-acting beta-agonist in the past three months, or any other significant disease.

The primary efficacy endpoint was the average FEV_1 area under the curve from pre-dose to 12 hours post-dose (AUC_{0-12h}) on Day 43. Secondary endpoints were trough FEV_1 on Days 22 and 43 as well as peak FEV_1 on Day 43. Following a 2-week run-in period, qualified patients were randomized (1:1 ratio) to 6 weeks of therapy with tiotropium 18mcg once-daily via HandiHaler® or a combination of salmeterol 50mcg plus fluticasone 250mcg delivered via separate metered dose inhalers. During the course of the trial, use of anticholinergics, beta-agonists other than the provided rescue medication (salbutamol), antileukotrienes, oral or inhaled corticosteroids, long-acting theophylline preparations, or any other investigational drug was not allowed. However, use of twice-daily theophylline preparations and mucolytic agents was permitted if patients had been on stable doses for at least 6 weeks prior to the study participation. Also, for treatment of COPD exacerbations, increased doses of theophylline for ≤7 days, oral corticosteroid bursts for ≤14 days, or antibiotics if appropriate were permitted. Patients recorded the use of the rescue medication on their diary cards. Vitals were monitored and information about adverse effects collected at each study visit.

At screening and/or at randomization, FEV_1 and FVC parameters were collected before and 60 min after four puffs of ipratropium (20 mg/puff) and four puffs of salbutamol (100 mg/puff). In addition, spirometric measurements were performed immediately before dosing on Days 1 (baseline), 22 and 43 and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dose on Day 43. Of 107 patients, 56 were randomized to receive tiotropium and 51 to salmeterol plus fluticasone arm. The two treatment groups were not comparable with respect to several baseline characteristics including smoking history (longer in tiotropium patients), number of current smokers (greater in the tiotropium arm), and FEV_1 as well as FVC (both lower in the tiotropium group). As a result, there was a randomization bias against tiotropium. On Day 43, there was no significant difference in the mean FEV_1 AUC_{0-12h} between the tiotropium group and the salmeterol plus fluticasone arm (1.55L and 1.57L, respectively, P=0.63). Mean trough FEV_1 was significantly greater in the salmeterol plus fluticasone arm than in the tiotropium group on Day 22 (1.55L±0.03 versus 1.46L±0.03, respectively, P=0.03); however, this significance was not sustained through Day 43 (1.54L±0.03 versus 1.46L±0.03, respectively, P=0.07). Similarly, the difference between peak FEV_1 values on Day 43 was not significant (1.66L±0.04 versus 1.68L±0.03, respectively, P=0.77). The average use of rescue medication was comparable in the two treatment arms: 1.99 inhalations per day in the tiotropium group versus 2.03 inhalations per day in the salmeterol plus fluticasone group at baseline and for the duration of the trial (P>0.05).

The percentage of patients who experienced adverse events was similar: 41.1% in the tiotropium and 43.1% in the salmeterol plus fluticasone arm. The following non-serious adverse events were considered to be study drug-related: dry mouth (3.6% versus 3.9%), oropharyngeal candidiasis (0% versus 2.0%), and throat irritation (0% versus 3.9%) in the tiotropium and salmeterol plus fluticasone arms, respectively. Serious adverse events occurred in 3.6% of patients receiving tiotropium and 2.0% of patients randomized to salmeterol plus fluticasone; however, none of the serious adverse events were considered to be study drug-related. One patient (2.0%) in the salmeterol plus fluticasone group discontinued trial participation as a result of an adverse event. Finally, the differences in vital signs between the two treatment groups were not clinically relevant.

The results of these two trials are comparable and indicate that bronchodilation associated with once-daily tiotropium (18mcg) therapy is comparable to that observed with twice-daily salmeterol (50mcg) plus fluticasone (250 or 500 mcg) combination. However, additional large, long-term trials are still needed to ascertain these findings.

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UPLIFT Trial Results

The purpose of the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) clinical trial was to determine whether treatment with SPIRIVA HandiHaler reduces the rate of decline of FEV_1 over time in patients with COPD. It was a four-year randomized, double-blind, placebo-controlled, parallel group clinical trial involving thirty-seven countries (approximately 500 investigational sites), which enrolled approximately 6000 patients, with approximately 3000 receiving SPIRIVA.[1, 2] Both treatment groups were permitted the use of all other inhaled respiratory medications except for inhaled anticholinergics.

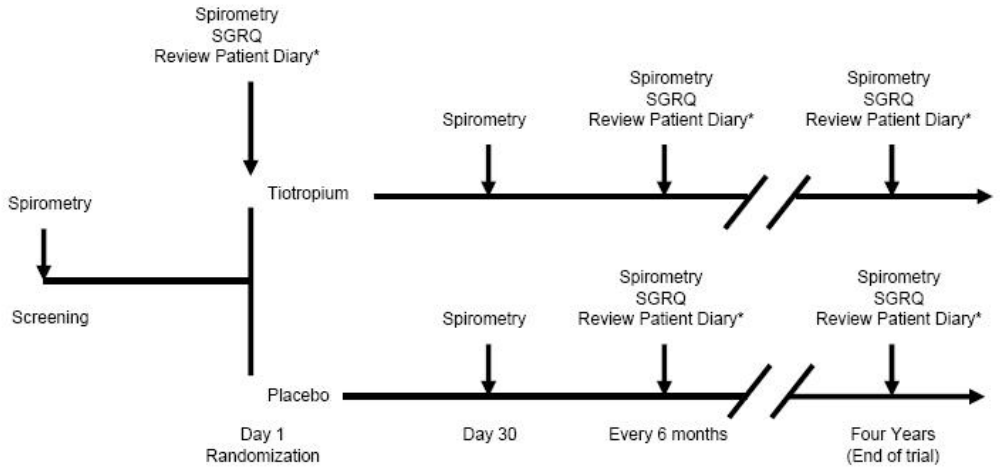
The co-primary endpoints were: (1) the yearly rate of decline in trough FEV_1 from Day 30 (steady state) until completion of double-blind treatment. Trough FEV_1 is the pre-dose value measured approximately 24 hours after the previous dose of study drug. (2) the yearly rate of decline in FEV_1 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from Day 30 (steady state) until completion of double-blind treatment.[1] Secondary endpoints included: (1) Mean yearly rate of decline in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and slow vital capacity (SVC) 90 minutes post ipratropium, including 30 minutes post albuterol inhalation, from Day 1 until completion of the trial (30 days post study treatment); (2) Mean yearly rate of decline in FVC and SVC 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from Day 30 until completion of double-blind treatment; (3) Mean yearly rate of decline in FEV_1, FVC and SVC prior to ipratropium and albuterol inhalation from day 1 until completion of the trial (30 days post study drug treatment); (4) Mean yearly rate of decline in trough FVC and SVC from Day 30 until completion of double-blind treatment (trough FVC and SVC are the pre-dose values measured approximately 24 hours after the previous dose of study drug); (5) Frequency of COPD exacerbations; (6) Time to first exacerbation; (7) Number of patients with COPD exacerbations; (8) Number of exacerbation days; (9) Number of patients with COPD exacerbations leading to hospitalizations; (10) Time to exacerbation leading to hospitalization; (11) Number of hospitalizations for exacerbations; (12) Number of days hospitalized for COPD exacerbations; (13) Mean yearly decline in SGRQ total score; (14) Mortality (respiratory and all-cause); (15) Adverse events.[1]

Patients were recruited into the trial if they were at least 40 years-old, had a clinical diagnosis of COPD, current or ex-smokers with a smoking history of ≥10 pack-years, a maximal post-bronchodilator FEV_1 ≤70% of predicted (European Community for Coal and Steel criteria[3]), FEV_1/FVC ratio ≤70%, and the ability to perform satisfactory spirometry. Presence or absence of reversibility was not a determining factor. The following exclusion criteria included: respiratory infection or an exacerbation of COPD in the four weeks prior to screening, a history of asthma or thoracotomy with pulmonary resection, use of supplemental oxygen >12 hours per day, or a significant disease other than COPD which, in the opinion of the investigator, may have influenced the results of the study or the patient's ability to participate in the study.

Following completion of the screening visit (Visit 1), patients entered a 2- to 4-week screening period, at the end of which those who qualified were randomized to tiotropium or placebo (Visit 2/Day 1).[1] The use of all previously prescribed respiratory medications, other than inhaled anticholinergics, was permitted if the prescriptions had not changed in the six weeks before randomization. There were no restrictions for medications used to treat exacerbations. Also, the pharmacological treatment for smoking cessation was allowed. All consented active smokers were advised by study personnel to discontinue smoking and were offered a smoking cessation program (e.g., counseling sessions, patient education and supportive literature); however, the participation in such a program was voluntary. Patients were seen one month after the initiation of trial treatment (Visit 3), at three months (Visit 4), and every three months thereafter until study completion (four years) or early discontinuation. Following the double-blinded treatment phase, patients received open-label ipratropium for 30 days. The final trial visit occurred 30 days after completion of the blinded treatment. The clinical trial design is depicted in Figure 1. Patients reported their smoking status at each visit. Safety data was monitored annually by an independent Data and Safety Monitoring Board (DSMB), which consisted of two pulmonologists, a cardiologist and, a biostatistician not associated with the study. As part of the mortality assessment, a Mortality Adjudication Committee was established to independently assess the cause of each death in the study.[1]

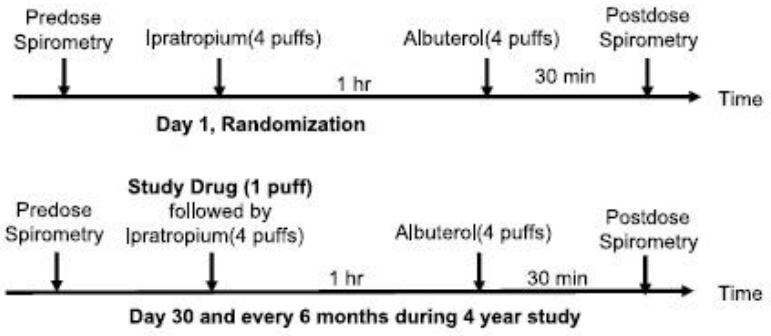
Spirometry was performed at screening and at 6-month intervals, pre- and post-bronchodilator, until the completion of the trial participation. After the pre-bronchodilator spirometry, four puffs of ipratropium bromide (80 mcg via MDI) were administered and four puffs of albuterol (400 mcg via MDI) 60 minutes later. The post-bronchodilator spirometry was performed 90 minutes after administration of ipratropium and 30 minutes after albuterol inhalation (see Figure 2). Following the randomization, the study drug was administered immediately before ipratropium and albuterol. The SVC was performed first, followed by the FVC. Identical spirometry systems with customized, study-specific software were used by all sites in order to standardize the spirometry. After each maneuver, the spirometry software provided immediate feedback regarding the acceptability and reproducibility (per ATS standards[4]). All maneuvers were stored electronically and transmitted for centralized quality assurance review.

Figure 1. UPLIFT: clinical trial design.



SGRQ, St. George's Respiratory Questionnaire
*Patient diary contains information on exacerbations, concomitant therapies, smoking status and adverse events since preceding visit.

Figure 2. Timing of study drug, ipratropium, and albuterol administration for pre- and post-bronchodilator spirometric evaluations at and following randomization.



Detailed information on COPD exacerbations and associated hospitalizations was collected at each study visit using a case report form specifically designed to capture all aspects of the COPD exacerbation(s). A COPD exacerbation was defined as an increase or new onset of more than one of the following respiratory symptoms: cough, sputum, sputum purulence, wheezing, dyspnea, with a duration of three or more days requiring treatment with an antibiotics and/or systemic (oral, intramuscular or intravenous) steroids. Exacerbations were categorized as mild, moderate or severe according to the following definitions:

- Mild – treated at home without seeing a healthcare professional.

- Moderate – requiring a visit with a healthcare provider (e.g., home visit, visit to an outpatient facility or an emergency department but not requiring a hospital admission).
- Severe – hospitalization (an emergency department stay >24 hours is considered a hospitalization).[1]

St. George's Respiratory Questionnaire (SGRQ) was used to assess health-related quality of life status.[5] To help ensure consistent understanding of the questionnaire at all study centers located in multiple countries, the SGRQ was administered in 27 different languages (all versions validated). Patients completed SGRQ prior to spirometry during the randomization visit and then every six months until completion of the double-blind phase of the study.

A random sample of 758 patients per group was determined to be needed to detect a difference of 15mL in the rate of decline between tiotropium and placebo at 5% level of significance and 90% power. For the primary analysis, patients need to have at least three observations from Day 30. Further, assuming a withdrawal rate of 35% and to allow for adequate sub-group analyses with adequate power, the sample size was determined to be 2,916 per treatment group. The primary endpoints were compared between the two treatment groups by performing random coefficient regression analysis. All randomized patients with at least three spirometry measurements on 3 separate test days per study protocol after randomization (corresponding at least one year of spirometry data) were included in this analysis. The effects of patients' baseline FEV_1, age, gender, and smoking status on the rate of FEV_1 decline were also investigated. The secondary spirometric endpoints and SGRQ total score were analyzed using the same approach. The number of exacerbations, associated hospitalizations, and exacerbation and hospitalization days per patient were normalized by extent of exposure and compared between the two treatment groups. The time to first exacerbation and associated hospitalization were also analyzed.

Trial participants were recruited between January 2003 and March 2004 and the trial was completed in February 2008. Over 8000 patients were screened and 5993 were randomized.[6] Of those randomized, 4383 (73%) completed 2 years, 3891 (65%) completed 3 years, and 3569 (60%) completed at least 45 months of trial. The median duration of treatment was 1436 and 1435 days in the tiotropium and placebo arms, respectively. A lower percent of patients did not complete at least 45 months of treatment in the tiotropium group (36.2%) than in the placebo arm group (44.6%, $P<0.001$).

The study groups were well balanced with respect to baseline characteristics and use of concomitant respiratory medications. The mean age was 65±8 years, approximately 75% of patient population was male and 30% were current smokers. The majority of trial participants were classified as having stage II (moderate) or III (severe) COPD (according to criteria of the Global Initiative for Chronic Obstructive Lung Disease [GOLD)]. Specifically, 46% of patients were classified as having stage II, 44% had stage III, and 9% of patients had stage IV disease. Over 90% of patients were receiving respiratory medications at baseline, which included long-acting beta-agonist and inhaled steroid (alone or in combination) use by 60% and 62%, respectively, in both treatment arms. Approximately 45% of patients were using short-acting anticholinergics at baseline. It is important to note that usual care prescription patterns reflecting current practices (other than non-treatment inhaled anticholinergics) were allowed in both the tiotropium and placebo arms. During the study, short-acting anticholinergics were only permitted for treatment of exacerbations if the physician deemed them necessary. In evaluating the use of maintenance medications during the study, an increase to about 72% use of long-acting beta-agonists and 74% use of inhaled steroids (alone or in combination), was seen in both the tiotropium and placebo groups.

The mean pre- and post-bronchodilator baseline spirometry results are summarized in Table 1.

Table 1. Mean pre- and post-bronchodilator baseline spirometry results[6].

Parameter	Pre-Bronchodilator		Post-Bronchodilator	
	Tiotropium (N=2986)	Placebo (N=3006)	Tiotropium (N= 2986)	Placebo (N=3006)
FEV_1 (L)	1.10±0.40	1.09±0.40	1.33±0.44	1.32±0.44
FEV_1 (% predicted)	39.5±12.0	39.3±11.9	47.7±12.7	47.4±12.6
FVC (L)	2.63±0.81	2.63±0.83	3.09±0.86	3.09±0.90
FEV_1/FVC Ratio	42.4±10.5	42.1±10.5	43.6±10.8	43.3±10.7

Plus–minus values are means ±SD.

Efficacy

Table 2 shows the results of the annual rate of decline in the mean FEV_1 (co-primary endpoints) and FVC, and SVC (secondary endpoints) values, pre- and post- bronchodilation from Day 30 until completion of the double-blind treatment (including 30 days after discontinuation of randomized treatment). The treatment set included patients with ≥3 post-randomization measurements. There were no statistically significant differences between tiotropium and placebo groups in the mean annual rate of decline.

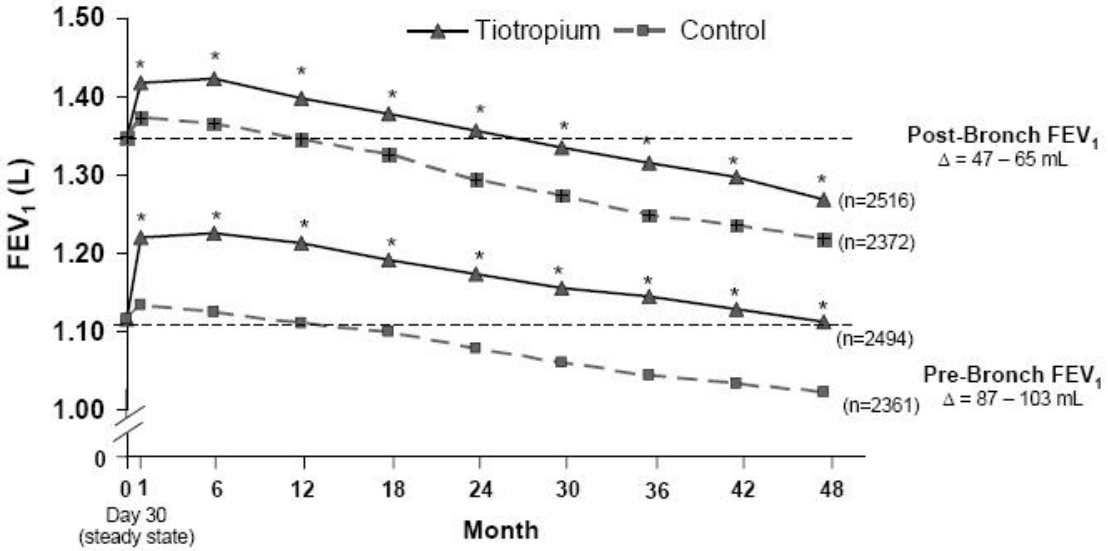
Table 2. Annual rate of decline in mean FEV_1, FVC, and SVC parameters pre- and post-bronchodilation (from Day 30 until the end of the study, including 30 days after randomized treatment).

Parameter	Tiotropium (mL/yr)		Placebo (mL/yr)		Difference	*P*-value*
	N	Mean±SE	N	Mean±SE	Mean±SE	
FEV_1						
Pre-bronchodilator	2557	30±1	2413	30±1	0±2	0.95
Post-bronchodilator	2554	40±1	2410	42±1	-2±2	0.21
FVC						
Pre-bronchodilator	2557	43±3	2413	39±3	4±4	0.30
Post-bronchodilator	2554	61±3	2410	61±3	1±4	0.84
SVC						
Pre-bronchodilator	2531	47±3	2374	41±3	6±4	0.11
Post-bronchodilator	2527	66±3	2383	65±3	1±4	0.79

* *P* values are unadjusted

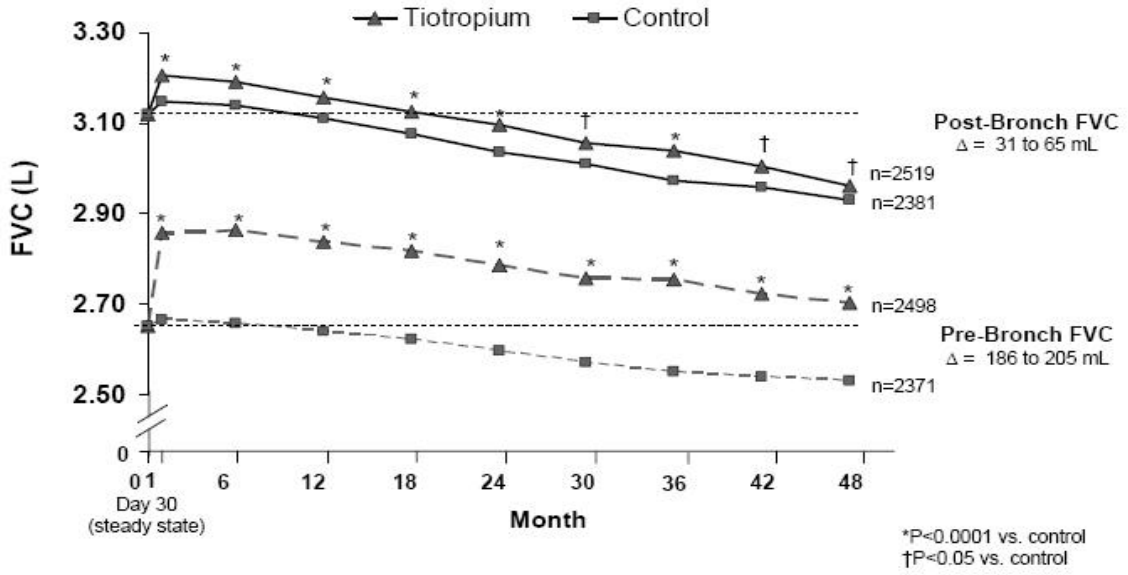
As depicted in Figures 3 and 4, compared with placebo, the mean FEV_1 and FVC values pre- and post-bronchodilation were significantly improved in patients receiving tiotropium and were maintained at all time points after randomization. Compared with placebo, the mean increases in FEV_1 in the tiotropium group for pre-bronchodilator values ranged from 87 to 103 mL and those for post-bronchodilator ranged from 47 to 65 mL ($P<0.001$). The mean increases in FVC in the tiotropium group, compared with placebo, for pre-bronchodilator values ranged from 186 to 205 mL and those for post-bronchodilator values ranged from 31 to 65 mL ($P<0.05$).

Figure 3. Mean pre- and post-bronchodilator FEV_1 values.



*P<0.0001 vs. placebo. Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements.
Baseline trough FEV_1 (observed mean) = 1.116L (trough), 1.347L (peak). Patients with ≥3 acceptable PFTs after day 30 were included in the analysis

Figure 4. Mean pre- and post-bronchodilator FVC values.

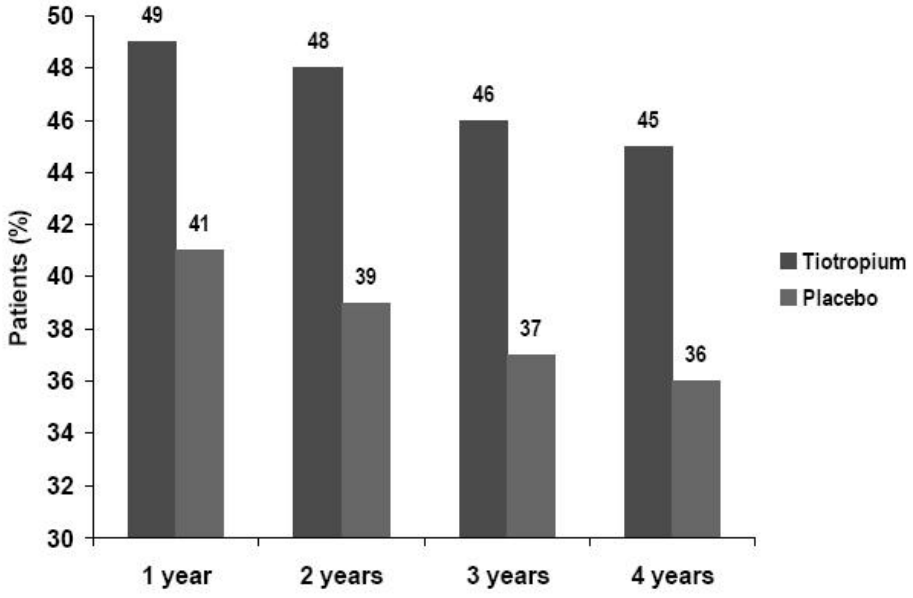


Analyses of the mean pre- and post-bronchodilator annual rate of decline in FEV_1 within pre-specified subgroups (age, gender, smoking status, GOLD stage, region, race, reversibility, BMI, and use of concomitant medications) did not show statistically significant differences between tiotropium and placebo except for the change in post-bronchodilator FEV_1 values in GOLD Stage II (moderate) subgroup (P=0.02). Also, a post-hoc analysis within a subgroup of patients who were not receiving either inhaled corticosteroids or long-acting beta-agonists at baseline (N=1554) revealed a statistically significant difference in the rate of decline in post-bronchodilator FEV_1 between tiotropium and placebo groups in favor of tiotropium (40±3mL and 47±3mL, respectively; P=0.046).

The rate of decline in the mean post-bronchodilator FEV_1 was lower in patients who completed the study period (38±1 ml per year in the tiotropium group and 40±1 ml per year in the placebo group) compared with those who discontinued study participation (55±4 ml per year in the tiotropium group and 57±4 ml per year in the placebo group).

The mean absolute change in SGRQ total score at all time points ranged from 2.3 to 3.3 units (P<0.001) in favor of tiotropium; however, these scores are below the 4 units previously determined to indicate a minimally clinically significant difference.[7] The overall mean difference between the tiotropium versus the placebo group was 2.7 units (95% CI, 2.0 to 3.3) in favor of tiotropium (P<0.001). As shown in Figure 5, there were larger percentages of patients achieving the 4-unit improvement in SGRQ total score compared to Day 1 in the tiotropium group compared with the placebo arm. The mean difference in the rate of decline of SGRQ scores between the tiotropium and placebo groups was not significant from 6 months to the end of the study.

Figure 5. Percentage of patients with ≥ 4-unit improvement in SGRQ total score*.



All P-values <0.001; *compared to Day 1

As seen in Table 3, there was a significant reduction in the mean number of exacerbations in the tiotropium group compared to the placebo group (14%, P<0.001). Tiotropium was associated with an 11% reduction in the mean number of exacerbation days (P=0.001). Also, the median time to first exacerbation was significantly delayed, 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group compared to the placebo group, 12.5 months (95% CI, 11.5 to 13.8). There was also a significant delay in the time to first hospitalization for an exacerbation in the tiotropium group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95, P=0.002). Neither the number of hospitalizations nor the number of hospitalization days per patient year, were statistically significant. The median time to first exacerbation treated with steroids or antibiotics was longer in the tiotropium group than the placebo group: 36.5 (95% CI 34.1 to 39.2) and 19.8 (95% CI 18.3 to 21.0) months versus 26.4 (95% CI 23.7 to 29.4) and 16.2 (95% CI 14.6 to 17.3) months, for tiotropium and placebo arms, respectively.

Table 3. COPD exacerbations and related hospitalizations*.

	Tiotropium	Placebo	Relative Risk Ratio for Tio vs. Placebo	95% CI	*P*-value
Exacerbations per patient-year†	0.73±0.02	0.85±0.02	0.86	0.81, 0.91	<0.001
Exacerbation days per patient-year†	12.1±0.32	13.6±0.35	0.89	0.83, 0.95	0.001
Exacerbation hospitalizations per patient-year†	0.15±0.01	0.16±0.01	0.94	0.82, 1.07	0.34
Exacerbation hospitalization days per patient- year†	3.17±0.17	3.13±0.17	1.01	0.87, 1.18	0.86
Total number of patients with exacerbations no. (%)§	2001 (67.0)	2049 (68.2)	N/A	N/A	0.35
Number of patients with exacerbations leading to hospitalizations no. (%)§	759 (25.4)	811 (27.0)	N/A	N/A	0.18

* Plus-minus values are means ±SE. N/A indicates not applicable.
† Relative risks calculated using Poisson regression corrected for treatment exposure and overdispersion.
§ These comparisons calculated using Fisher's exact test.

Safety

Patient safety was closely followed by an independent Data Safety Monitoring Board during this study with vital status (at least 45 months of follow-up, and patients who discontinued treatment) assessed in 98% of patients receiving tiotropium and 97% of patients randomized to placebo. The incidence of adverse events reported in tiotropium and placebo groups were comparable: 92.6% and 92.3%, respectively. The most commonly reported adverse events were related to the lower respiratory system and included COPD exacerbations, pneumonia, and dyspnea. Adverse events such as dry mouth and constipation, which are consistent with known anticholinergic properties of tiotropium were also observed. The incidence rate of adverse events reported by >3% of patients in any treatment group during the treatment period (from first to last day of study drug + 30 days) is summarized in Table 4.

Table 4. Incidence rate (per 100 patient years) of patients experiencing adverse events reported by >3% of patients in any treatment group during the treatment period (from first to last day of study drug + 30 days).

Adverse Event	Placebo n=3,006	Tiotropium n=2,986	Rate Ratio (Tio/Pla)	95 % CI
Abdominal pain	1.12	1.22	1.09	0.83, 1.43
Arthralgia	1.10	1.36	1.24	0.95, 1.62
Atrial Fibrillation	1.32	1.28	0.97	0.75, 1.26
Back pain	2.25	2.18	0.97	0.79, 1.18
Benign prostatic hyperplasia	1.12	1.32	1.18	0.90, 1.54
Bronchitis	2.82	2.57	0.91	0.76, 1.10
COPD exacerbations	45.5	38.0	0.84	0.79, 0.89
Cataract	1.45	1.30	0.90	0.70, 1.15
Constipation	1.29	1.63	1.26	0.99, 1.61
Cough	2.57	2.64	1.03	0.86, 1.24
Depression	1.14	1.42	1.25	0.96, 1.62
Diarrhea	1.43	1.50	1.04	0.82, 1.33
Dizziness	0.94	1.11	1.18	0.88, 1.58
Dyspnoea	5.49	4.09	0.75	0.65, 0.86
Headache	1.61	1.88	1.17	0.94, 1.47
Hypercholesterolemia	1.13	1.12	0.99	0.75, 1.31
Hypertension	3.45	3.08	0.89	0.75, 1.05
Influenza	1.87	1.73	0.92	0.74, 1.15
Insomnia	1.06	1.42	1.34	1.02, 1.75
Mouth dry	0.93	1.68	1.80	1.37, 2.36
Nasopharyngitis	4.06	4.33	1.07	0.92, 1.24
Nausea	1.09	1.00	0.91	0.69, 1.22
Edema	1.52	1.57	1.03	0.82, 1.31
Pneumonia	5.14	4.94	0.96	0.84, 1.10
Respiratory failure	1.39	0.94	0.67	0.51, 0.89
Rhinitis	1.32	1.09	0.83	0.63, 1.08
Sinusitis	1.90	2.14	1.12	0.91, 1.39
Upper respiratory tract infections	3.57	3.38	0.95	0.81, 1.11
Urinary tract infections	2.00	2.08	1.04	0.85, 1.28

The serious adverse events reported by greater than 1% of patients were either of cardiac or respiratory origin and were more frequent in the placebo group (Table 5). Overall, serious adverse events were reported by 51.6% of tiotropium and 50.2% of placebo patients.

Table 5. Serious adverse events incidence (per 100 pt-yrs) reported by >1% in any treatment group[6]**.

Serious Adverse Even	Relative Risk (Tio/Placebo)	95% CI
Cardiac System Organ Class (SOC)	0.84	0.73, 0.98*
Angina	1.44	0.91, 2.26
Atrial fibrillation	0.95	0.68, 1.33
Cardiac failure	1.25	0.84, 1.87
Cardiac failure congestive	0.59	0.37, 0.96*
Coronary artery disease	0.58	0.33, 1.01
Myocardial infarction	0.71	0.52, 0.99*
Respiratory (lower) SOC	0.84	0.77, 0.92*
Bronchitis	1.20	0.73, 1.98
COPD exacerbation	0.84	0.76, 0.94*
Dyspnea	0.61	0.40, 0.94*
Pneumonia	0.95	0.81, 1.11
Respiratory failure	0.69	0.52, 0.92*

*P<0.05; **excluding lung cancer (multiple different terms)

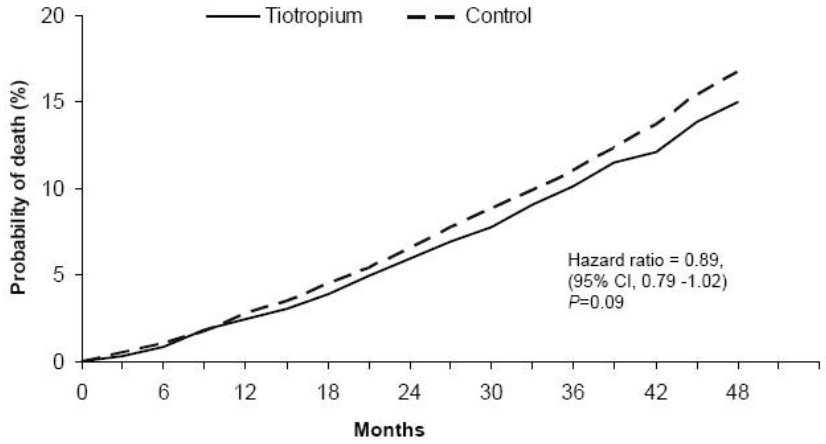
Summarized in Table 6 are the UPLIFT findings on the incidences of stroke and myocardial infarction.

Table 6. Incidence of stroke and myocardial infarction[6].

Adverse Event	Tiotropium (N=2986)		Placebo (N=3006)		Risk Ratio	95% CI
	N with event	Rate / 100pt-yrs	N with event	Rate / 100pt-yrs		
Stroke	82	0.88	80	0.93	0.95	0.70,1.29
Serious	66	0.70	63	0.73	0.97	0.69,1.37
Fatal (on treatment-adj.)	12	0.13	13	0.15	0.85	0.39,1.87
Myocardial Infarction	67	0.71	85	0.98	0.73	0.53,1.00
Serious	65	0.69	84	0.97	0.71	0.52,0.99
Fatal (on treatment-adj.)	9	0.10	8	0.09	1.04	0.40,2.69

There was no increased risk in all-cause mortality. Figure 6 shows Kaplan-Meier estimates of the probability of death from any cause. During the four year trial period plus the 30-day follow-up period, there were 941 deaths (intention-to-treat analysis, vital status information included). Of those, 14.9% occurred in the tiotropium arm and 16.5% in the placebo group (HR, 0.89; 95% CI, 0.79 to 1.02). During the four year trial period alone (1440 days), 921 fatal events occurred (intention-to-treat analysis, vital status information included). Among those, 14.4% were in the tiotropium group and 16.3% in the placebo arm (HR, 0.87; 95% CI, 0.76 to 0.99).

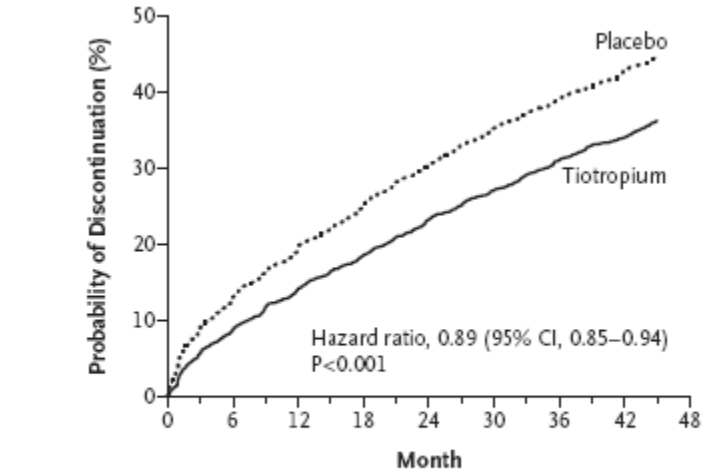
Figure 6. Kaplan-Meier estimates of the probability of death from any cause.



According to the on-treatment analysis, there were 381 fatal events (12.8% of patients) in the tiotropium arm and 411 (13.7% of patients) deaths in the placebo group (HR, 0.84; 95% CI, 0.73 to 0.97). In the on-treatment group, there were 24 cardiac deaths in the tiotropium group and 25 cardiac related deaths in the placebo group, all of which were adjudicated.

The probability of trial discontinuation was higher in the placebo arm compared with the tiotropium group: HR, 0.89; 95% CI, 0.85–0.94; *P*<0.001 (Figure 7). Adverse events were the most common reason for trial discontinuation with 24% of patients in the placebo arm and 21% of patients in the tiotropium group prematurely discontinuing trial participation as a result.

Figure 7. Probability of trial discontinuation.



In summary, the results of the UPLIFT trial, during which use of all previously prescribed respiratory medications, other than inhaled anticholinergics, was permitted, show no effect on the rate of decline of pre- or post-

bronchodilator FEV_1 of tiotropium versus placebo. The mean FEV_1 and FVC values pre- and post-bronchodilation were significantly improved in patients receiving tiotropium compared with placebo and were maintained at all time points after randomization. While improvement in FEV_1, FVC, and SVC were maintained throughout the study, there was no effect on the rate of decline of FVC and SVC. SGRQ total scores were improved throughout the study, but the tiotropium group was similar to baseline after 4 years of treatment. There was a reduction in exacerbations and hospitalizations. The UPLIFT safety data show that treatment with tiotropium was associated with no increased mortality risk, no increased cardiac morbidity risk, no increased stroke or myocardial infarction risk, no increased lower respiratory morbidity risk, and no increased risk of respiratory failure.

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Use in Patients with Mild-to-Moderate COPD

A 12 week, randomized, double-blind, parallel group, multi-center study was conducted by Johansson and colleagues[1] to evaluate the efficacy of tiotropium 18 mcg delivered via HandiHaler® in patients with mild COPD according to the 2003 Swedish Guidelines[2] (mild to moderate COPD according to the 2007 GOLD guidelines[3]). The study was conducted in 27 centers in Sweden, from March 2004 to July 2005. Inclusion criteria were: age of at least 40 years, a diagnosis of mild COPD according to the 2003 Swedish Guideline (post-bronchodilator FEV_1/FVC <70 % and FEV_1 ≥60 % predicted); smoking history ≥10 pack-years, and a Medical Research Counsel (MRC) dyspnea score ≥2. The following criteria were exclusionary: history of asthma; allergic rhinitis or atopy; blood eosinophil count ≥600/mm^3; lower respiratory tract infection or an exacerbation in the last six weeks; myocardial infraction in the last six months; unstable cardiac arrhythmia; regular oxygen use; use of oral or inhaled steroids in the past three months or any other significant disease.

The primary endpoint was change in FEV_1 area under the curve from pre-dose to 2 hours after dose (AUC_{0-2h}) from baseline to 12 weeks. Other endpoints were trough FEV_1 and FVC, use of rescue medication, and adverse events. After completing a screening visit, patients entered a two week run-in period. Subsequently, on Day 1 of the study, eligible patients were randomized to either placebo or tiotropium. Spirometry was performed at screening, on Day 1, 15 (2 weeks), and 85 (12 weeks). Pre-dose measurements on Day 1 were considered baseline. FEV_1 and FVC were collected 10 minutes before, 0.5, 1 and 2 hours after dose. Trough FEV_1 and FVC were the pre-dose responses on Day 15 and 85. Patients completed dyspnea and health-related quality of life (HRQL) questionnaires at the beginning and at the end of the trial (Day 85). The severity of dyspnea was evaluated using baseline dyspnea index (BDI) and the MRC dyspnea scale. Instead of using the transitional dyspnea index at the end of the trial, BDI was used as an exploratory measure. The European Quality of Life Questionnaire (EQ-5D) was used to assess the HRQL. During the course of the trial, use of short-acting anticholinergics, beta-agonists other than the provided rescue medication (salbutamol), oral or inhaled corticosteroids, and theophylline was not allowed. However, for treatment of a COPD exacerbation, corticosteroids and antibiotics for ≤2 weeks, or theophylline for ≤7 days were permitted. Patients recorded adverse events, including COPD exacerbations, and the use of rescue medication.

There were 224 patients enrolled in this trial, with 107 randomized to the tiotropium group and 117 to placebo. Majority of the trial participants had either mild or moderate COPD: 28.2% mild, 68.6% moderate, and 3.2% severe (according to the 2007 GOLD guidelines). Baseline spirometric parameters of both groups were comparable. With respect to demographic characteristics, the percentage of male patients in the tiotropium group was greater than in the placebo arm (53% versus 43%, respectively). Also, about 57% of patients in the tiotropium group were current smokers compared with 63% in the placebo group. The difference between tiotropium and placebo groups in adjusted mean changes from baseline of spirometric parameters on Days 1, 15, and 85 is summarized in Table 1 below.

Table 1. Adjusted mean change from baseline of spirometric parameters: tiotropium versus placebo group.

Parameter (mL)	***Day 1***		***Day 15***		***Day 85***	
	Difference	***P***	***Difference***	***P***	***Difference***	***P***
FEV_1 AUC_{0-2h}	74±15	<0.0001	172±22	<0.0001	166±26	<0.0001
FVC AUC_{0-2h}	89±27	<0.01	182±37	<0.0001	160±43	<0.001
Trough FEV_1	NA	NA	109±20	<0.0001	118±31	<0.001
Trough FVC	NA	NA	178±36	<0.0001	187±50	<0.001

During the trial, use of rescue medication decreased in both treatment arms. Patients in the tiotropium arm used fewer inhalations of rescue medication in all 12 weeks of the trial and significantly fewer doses per day during Weeks 1 to 5 and Week 9 than patients receiving placebo (P<0.05). No statistically significant difference was observed

between tiotropium and placebo in BDI focal score (BDI score in the tiotropium arm was numerically higher than that in the placebo group), MRC dyspnea score, or the EQ-5D questionnaire total score. Of note, the investigators remarked about the following: (1) the trial was not powered to detect differences in HRQL (seen between placebo and tiotropium groups in previous trials) or change in BDI, (2) its duration may have been too short to for any differences in HRQL to become significant, and (3) use of a generic tool such as EQ-5D rather than a more sensitive, disease-specific St. George's Respiratory Questionnaire (SGRQ), may have not been ideal for detecting HRQL changes in patients with milder COPD.

The incidence of adverse events was comparable in both study arms (46.7% in the tiotropium and 41.9% in the placebo group). Two patients from the placebo group withdrew as a result of an adverse event. Bronchitis and COPD exacerbation rates were lower in the tiotropium group compared with the placebo arm (0.9% versus 3.4% and 1.9% versus 3.4%, respectively). However, cough and pneumonia were more frequent among patients randomized to tiotropium (2.8% versus 1.7% and 2.8% versus none, respectively). Nasopharyngitis was the most frequently reported upper respiratory system disorder. It was experienced by 15.9% of patients treated with tiotropium and 15.4% of patients in the placebo group. Greater percentage of patients in the tiotropium arm experienced serious adverse events compared with the placebo group (2.8% versus 0.9%, respectively); however, none of these events were considered to be related to the study drug.

The investigators concluded that tiotropium improves lung function in patients with mild to moderate COPD, although further studies are required to confirm the long-term benefit.

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